

**REMARKS**

Applicant respectfully requests reconsideration. Claims 1-5, 8-20, 22, 27-32, 43, 45-57, 63-65, 70-73, 76-80, 83, 84, 88, 89, 94, 95, 97 and 99 are pending in this application with claim 1 being an independent claim. Claims 5, 13, 15, 45-57, 63-65, 70-73, 76-80, 83-84, 88-89, 94-95 and 97 are currently withdrawn. Upon allowance of claim 1, reconsideration and in some cases rejoinder of the withdrawn claims is requested. Claims 1, 2 and 45 are amended to provide proper antecedent basis for dependent claims.

No new matter has been added.

***Double Patenting Rejection***

The Examiner has provisionally rejected claims 1-4, 8-11, 16-20, 22, 29-32, 43 and 99 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 41-46, 52-56 and 58-60 of co-pending Application No. 10/816,220.

In the previous response, Applicant deferred substantive rebuttal of the rejection until the cited application is allowed. The Examiner now states that “the provisional rejection is maintained until a properly filed terminal disclaimer has been received or the claims have been amended sufficient to obviate this provisional rejection”. MPEP 804(I)(B) states that “the merits of such a provisional rejection *can* be addressed by both the applicant and the examiner without waiting for the first patent to issue” (emphasis added). Notably, the MPEP does not require that the merits *must* be addressed in such a situation. Moreover, the MPEP also states that “the ‘provisional’ double patent rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that ‘provisional’ double patenting rejection is the only rejection remaining ...”. *Id.* At that point, the examiner must withdraw the provisional rejection and allow the claims. Consistent with this practice, Applicant defers substantive rebuttal of the provisional rejection until the cited co-pending application is allowed, and in the alternative requests withdrawal of the rejection once it is the only remaining rejection.

***Rejection under 35 U.S.C. §112, enablement***

The Examiner has rejected claims 1-4, 8-12, 14, 16-20, 22, 29-32, 43 and 99 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement, i.e., the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

Applicant respectfully traverses for the reasons set forth below.

**I. Enablement of composition claims.**

The test of the enablement requirement is “whether the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention”. MPEP 2164.01. The evidence of enablement must be commensurate in scope with the claimed invention.

The pending claims are composition claims. Claim 1, the only independent claim currently being considered, is directed to a composition comprising an immunostimulatory nucleic acid comprising a defined nucleic acid sequence of SEQ ID NO:1. This nucleic acid molecule is a CpG nucleic acid; CpG nucleic acid were known to be immunostimulatory prior to the filing date.

The Examiner acknowledges that the claimed compositions can be made, but challenges that the compositions can be used. MPEP 2164.01(c) states that for a composition claim that is not limited by a recited use (i.e., a use recited in the claim), then “any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use”. Furthermore, “if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention”. *Id.* The specification discloses multiple uses for the claimed compositions. For example, the specification states that the claimed nucleic acids can be used to stimulate immune responses *in vivo* and *in vitro*, such as stimulating B-cells, NK T cells, and antigen-specific antibodies. *See*, Figs. 1, 6, 7, 14, 15 and 16. The specification further teaches that, *in some embodiments*, the claimed nucleic acids can be used to treat infection, cancer, allergy and asthma. The specification further *demonstrates* immune stimulation by the claimed compositions, including *in vitro* and *in vivo* antigen specific

and antigen non-specific responses. *See Examples and Figs. 1-16.* Therefore, under the standard set forth in MPEP 2164.01(c), the specification enables the claimed compositions.

The basis of the rejection relies on an improper construction of the claims. The Examiner has incorrectly characterized the claimed invention as relating to “a composition comprising (or consisting of) SEQ ID NO:1 … (that) also comprises cancer antigen (sic) … as well as anti-cancer agents”. The Examiner infers that “the intended use of the claimed composition is for in vivo use in a method to treat cancer in a subject”. In doing so, the Examiner imputes an unrecited functional limitation (i.e., the treatment of cancer) to all the pending claims. This is improper. Comark Communication, Inc. v. Harris Corp., 156 F.3d 1182 (Fed. Cir., 1998).

At the outset, Applicant notes that a *prima facie* case of non-enablement of claims 2, 9-11, 16-20, 22, 27-32, 43 and 99 has not been made at least because none of these claims recites the elected cancer antigen or anti-cancer therapy. Thus, at a minimum, the Examiner is requested to reconsider and withdraw the rejection of this set of claims or to elaborate on why the use of such claims is not enabled.

The Examiner takes issue with claims 4, 12 and 14 which recite either an antigen (including the elected species of cancer antigen) or a therapeutic agent (including the elected species of anti-cancer agent) and is requiring evidence of anti-cancer therapeutic efficacy for enablement of these claims. Respectfully, the Examiner is requiring an enablement standard that is higher than that required by the law. None of the pending claims, including claims 4, 12 and 14, recites “treating cancer” as a functional limitation and thus none of the claims should be so construed. Enabling uses of such claims should not be restricted to an in vivo therapeutic use. Rather, the specification contemplates use of these compositions in vitro or in vivo in non-human subjects and for non-therapeutic purposes. For example, the claimed nucleic acids and an antigen (as recited in claim 4) can be used to produce high titer antibodies against the cancer antigen in mice, as taught in the specification. *See Example 2 at pg. 92, lines 5-10, and Figs. 15-16.*

## II. Wands analysis and predictability in the art.

Applicant previously presented a Wands analysis in support of enablement of the claimed compositions. In response, the Examiner asserts that “the state of the art *with regard to cancer* is

unpredictable" (emphasis added). Applicant notes the Examiner's emphasis on unpredictability in the art. There is no evidence that the Examiner has considered the Wands factors as a whole, as legally required. Rather it appears that the Examiner has improperly considered the issue of unpredictability to be dispositive. *See In re Wands*, 858 F.2d 731.

Applicant further notes that the unpredictability alleged by the Examiner is in the art of *cancer immunotherapy*. As stated above, the Examiner has disregarded the disclosed and exemplified uses for the claimed compositions, both in the presence and absence of antigen, and thus the emphasis on unpredictability in the art of cancer immunotherapy is improper. The claimed compositions can be used for immunostimulation in general, whether in vitro or in vivo, whether in human or non-human subjects, and whether for therapeutic or other purposes. Accordingly, unpredictability in the art of cancer immunotherapy does not negate enablement of compositions having another exemplified use.

Notwithstanding this, and rather for the record, Applicant respectfully traverses the Examiner's assertion of unpredictability in the art.

a. CpG nucleic acids are immunostimulatory.

The instant disclosure and the state of the art present sufficient evidence showing that CpG nucleic acids are immunostimulatory. Examples 1 and 2 of the specification demonstrate that the claimed composition can stimulate immune responses both in vivo and in vitro. *See* pgs. 88-98. In particular, when administered to mice in combination with the HBsAg, the composition can induce both humoral and cell-mediated anti-viral antigen-specific immune responses. Such responses would be useful for treatment of viral infections.

The Examiner cites a number of references to support unpredictability of CpG induced immunostimulation. Applicant addresses each below.

McCluskie et al. (Vaccine (2001) 19:2657-2660) is cited for the proposition that "T-rich immunostimulatory nucleic acids do not induce an immune response". McCluskie et al. does not disclose a nucleic acid having the sequence of SEQ ID NO:1 and therefore its teachings are not relevant to the claimed invention. However, regardless, Applicant notes that the CpG nucleic acid analyzed by McCluskie et al. (i.e., 1826) did induce an immune response, thereby demonstrating immunostimulation by CpG nucleic acids.

The Examiner makes the unsupported statement that “in vitro animal model studies have not correlated well with in vivo clinical trial results in patients thereby questioning the value of such in vitro animal models as predictors of in vivo human responses”. *See OA pg 5.* The specification however demonstrates immune stimulation of human cells in vitro.

McCluskie et al. (Mol. Med. (1999) 5(5):287-300) is cited for the proposition that “biological responses of CpG ODN vary, depending on the routes of administration and the organism”. *See OA pg 6.* McCluskie et al. is an article describing DNA vaccines (i.e., vaccines in which an antigen or other protein is encoded by a plasmid or other nucleic acid vector) against Hepatitis B virus. The reference teaches that the response to the DNA vaccine varies according to the mode of delivery and the organism. The claimed invention relates to particular CpG nucleic acids. The issues of predictability and therapeutic efficacy are different for CpG nucleic acids and DNA vaccines. Accordingly, the teachings of McCluskie et al. are not relevant to the claimed invention.

Krieg et al. (Immunology Today (2000) 21:521-526) is cited to support the same proposition, however, Applicant could not find support for the Examiner’s position at the indicated page. Instead, page 524 teaches that “studies have shown CpG ODN … to be effective with multiple types of antigens and routes of immunization, including mucosal immunization”, and that “[u]nlike many vaccine adjuvants that have been extremely effective in mice but disappointing in humans, CpG DNA is also highly effective in higher primates”. These teachings support the consistency of an induced response in different organisms and using different administration routes.

The Examiner further questions the safety of CpG nucleic acids in vivo. To this end, Krieg et al. (Immunology Today (2000) 21(10):521-526) on page 524 teaches, with reference to potential side effects induced by CpG nucleic acids, that the “magnitude of cytokine response to CpG is much greater in mouse cells than in human or monkey cells”. The reference therefore stands for the proposition that the likelihood and severity of side effects such as SIRS are expected *to be less in humans than in mice*. Such disparity is clinically beneficial.

Wohlleben et al. (Trends in Immunology (2001) 22(11):618-626) is cited for the proposition that CpG ODN therapy may be associated with septic shock in mice, development of autoimmune disease, and activation of residual auto-reactive T cells. However, a further reading

of the reference provides the statement that “it is totally unclear if this can also occur in healthy rodents or, more importantly, humans”. The reference further documents successful use of CpG ODNs as a vaccine against atopic disorders. *See* pg. 629 right column.

Applicant notes that the issue of whether a drug is safe and has no side effects is not an appropriate test for enablement. MPEP 2164.01(c) states that “the applicant need not demonstrate that the invention is completely safe”. One cannot possibly determine the parameters of safety without a controlled clinical trial, and it is well established that a clinical trial is not required for enablement. *See In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995).

Weiner et al. (J. Leuk. Biol. (2000) 68:456-463) is cited for the proposition that “the molecular mechanisms of CpG oligonucleotides’ immunostimulatory effects are not yet understood” and “not all CpG ODN are alike and more needs to be learned about the heterogeneous responses that occur based on host organism, cell subset, or CpG ODN sequence”. The Examiner’s reasons for citing Weiner et al. appear inapplicable to the claimed invention and the instant specification for a number of reasons. First, understanding mechanism is not a prerequisite to patentability. Second, the claimed invention does not relate to *any* CpG ODN, but rather a family of ODN having at least a 24 nucleotide consensus sequence (i.e., SEQ ID NO:1) to which immunostimulatory activity is attributed. And third, the instant Examples show that the claimed nucleic acids stimulate mouse and human immune cells including B and NK cells, both of which are important in an anti-cancer response, as documented by Weiner et al.

Regardless, the reference summarizes the immunostimulatory activity of CpG nucleic acids, and therefore actually argues for, rather than against, predictability in the CpG nucleic acid art. The reference teaches that there is a correlation between the in vitro and in vivo immunostimulatory effects observed with CpG nucleic acids. *See* pg. 457, right column, third paragraph. The reference discloses that CpG ODNs induce cytokines and activate immune cell subpopulations involved in anti-tumor immunity. *See* pg. 460, right column, second paragraph. The reference further discloses that CpG nucleic acids induce an antigen-specific antibody response and protection against subsequent tumor challenge in a murine tumor model. *See* pg. 458, right column, last paragraph. The claimed nucleic acids, including CpG ODN 10106, possess similar immunostimulatory profiles as those described by Weiner et al., including B and NK cell activation, antigen-specific antibody production, and IP-10, IL-10 and IFN- $\alpha$  secretion.

The reference further states that “studies to date suggest CpG DNA could have significant therapeutic promise in the treatment of a variety of disorders, including infectious disease, allergy, and cancer” and “extensive studies have been done in rodents, and some studies have been done in non-human primates. The observed in vivo data fit well with the in vitro data outlined above”. *See* pgs. 456 and 457.

Agrawal et al. (Mol. Med. Today (2000) 6:72-81) is cited for the proposition that “the incorporation and positioning of chemical modification of nucleotides relative to the CpG dinucleotide are highly unpredictable”. Agrawal et al. is an article summarizing antisense oligonucleotide therapy. The reference suggests that in order to reduce non-antisense related activity of antisense ODN, CpG motifs should be avoided or at least mutated to their methyl forms. *See* pg. 78. The claimed nucleic acids comprise a defined nucleic acid sequence having a fixed number (and location) of CpG dinucleotides. The teachings of the reference relating to positioning and chemical modification of the nucleotides are therefore not relevant to the claimed nucleic acids. The reference acknowledges rather than refutes the immunostimulatory effect of CpG nucleic acids.

b. CpG nucleic acids in cancer immunotherapy.

Certain CpG nucleic acids have been demonstrated to induce anti-cancer immune responses. The references provided in Appendix A of the previous response demonstrate that certain CpG nucleic acids have therapeutic utility in the treatment of cancers. CpG ODN 7909 which is described in the Examples as surprisingly having similar immune stimulatory profiles to the claimed nucleic acids is currently in two phase III clinical studies for the treatment of first-line non-small cell lung cancer. The corresponding phase II clinical study demonstrated a survival benefit for patients receiving CpG 7909 in combination with chemotherapy. In another on-going phase I/II clinical trial, patients with metastatic MAGE-3 positive melanoma are being vaccinated with CpG 7909 and MAGE-3 antigen to evaluate safety, tolerability, immunogenicity, and anti-tumor activity. van Ojik et al., Ann. Oncol. (2003) 13:157. Immunological analysis thus far has showed an increase (10-150x) in anti-MAGE-3 antibody titers in these patients. Speiser et al. showed that CpG 7909, when administered with melanoma antigen A, induced rapid and robust antigen-specific T cell responses in melanoma patients. J

Clin. Invest. (2005) 115:739-746. Schneeberger et al. reported that CpG motifs are efficient adjuvants for a melanoma antigen DNA cancer vaccine in the Cloudman M3/DBA/2 model. J. Invest Dermatol. (2004) 123:371-379. These data demonstrate that certain CpG nucleic acids are, at a minimum, immunostimulatory in a cancer context.

Krieg et al. (Pharmacology and Therapeutics (1999) 84:113-120) and Ballas et al. (J. Immunology (2001) 167:4878-4886) are recited to support the unpredictability of CpG ODN in cancer treatment. Krieg et al. is cited for the teaching that although “CpG has NK-stimulating properties ... many or even most types of tumors are relatively resistant to NK-mediated lysis”. Applicant points out that NK cell activation is but one element of the immune response induced by CpG nucleic acids, and that other elements of that response are also useful in anti-tumor immunity (e.g., B cell activation and cytokine induction). See e.g., Weiner et al. discussed herein. Krieg et al. further disclose that activation of NK cells with CpG nucleic acids prior to treatment with monoclonal antibody enhances their efficacy in anti-cancer treatment. *See* pg. 117, right column, last paragraph. Thus, even for tumors resistant to NK-mediated lysis, treatment with tumor-specific monoclonal antibodies and CpG nucleic acids was successful. The reference therefore does not stand for the proposition that CpG nucleic acids are ineffective in tumor immunotherapy.

Ballas et al. is cited for the teaching that a single CpG ODN cannot be used to treat all cancers and tumors. However, the Examiner acknowledges that Ballas et al. teaches that “CpG motifs can be custom-tailored for each desired immune effect” and that some CpG nucleic acids activate NK cells and are effective as a sole therapeutic agent at preventing the development of B16 melanoma. The reference demonstrates that mice injected with B16 tumor have increased survival when treated with CpG ODN. *See* pg. 4880, left column. The reference concludes that rejection of the B16 tumor was due to the ability of CpG ODN to augment the killing activity of NK cells. *See* pg. 4882, right column. Applicant points out that CpG ODN 10106 demonstrates an immune response profile similar to that of CpG 7909, a CpG nucleic acid with demonstrated broad anti-cancer effects. *See* references discussed herein.

c. Cancer immunotherapy generally.

The Examiner cites a number of references in support of the unpredictability in cancer immunotherapy generally.

Ezzell and Forni et al. are cited for the proposition that “tumor cells *in vivo* simply do not display their unique antigens in ways that are easily recognized by cytotoxic T lymphocytes”. As stated previously, the claimed nucleic acids induce antigen-specific as well as innate (antigen-non-specific) immune responses. Notwithstanding the teachings of these references however the Examiner must also consider the references described herein that document the effect of certain CpG nucleic acids in cancer treatments, including in vaccine settings.

Chatterjee et al. (Cancer Immunol Immunother. (1994) 38:75-82) is cited for the proposition that “it has been an art-recognized experience that for any novel therapy, the transition from the laboratory to the clinic (animal experiments to the bedside) is a quantum leap”. The Chatterjee et al. reference is directed to anti-idiotypic antibody therapy and not immunostimulatory nucleic acid based therapy. The cited statement also refers to “novel” therapies presumably meaning therapies that have not been tested in human subjects. Again, this is not the case with CpG nucleic acids. The significance of Chatterjee et al. to the claimed invention is tenuous at best.

The Examiner asserts that cancer vaccine technology is unpredictable and cites Donnelly (Nat. Med. (2003) 9(11):1354-1356), DeGruyl et al. (Nat. Med. (1999) 5(10):1124-1125), and Bitton (Curr. Opin. Mol. Therap. (2004) 6(1):17-25) in support thereof. Donnelly however states that “significant progress is being made, reflected in the number of successful phase 1 and 2 clinical trials.” Indeed, the reference details the successful use of a vaccine together with all-trans retinoic acid (an anti-cancer agent) in the treatment of acute promyelocytic leukemia, and concludes that “synergy between the immunotherapy and conventional chemotherapy” was shown. Moreover, the reference further states that vaccines used in combination with cytokines have been more successful than vaccines used alone. To this end, Applicant points out that the claimed nucleic acids stimulate cytokines. *See Examples 1 and 2 and Figs. 2-4, 8-10 and 13.* Accordingly, the teachings of Donnelly, when taken as a whole, support rather than refute enablement of the claimed invention.

DeGruijl et al. is cited for the teaching that although “a variety of anti-tumor vaccine clinical trials have been undertaken … there has been little evidence of clinical efficacy.” However, the point of the reference is improvements in cancer vaccine strategies over pre-1999 strategies. For example, the reference describes a clinical trial by Bendandi et al. as making a “large advance over previous tumor vaccines” and having “benefited from the advances made in our understanding of anti-tumor immunity.” The filing date of the claimed invention is at least two years after the DeGruijl et al. reference and accordingly the claimed invention must be viewed with light of the “large advances” made in anti-tumor immunity, including anti-tumor vaccines, which are supportive of immunotherapy in the treatment of cancer.

Bitton et al. is cited for the teaching that therapeutic vaccines have little use in cancer treatment. However, Bitton et al. documents successful vaccines, such as human papillomavirus (HPV)-16 vaccine and hepatitis B virus (HBV) vaccine. *See* pg. 18, left column, third paragraph. Importantly, the role of immunostimulatory nucleic acids, such as those currently claimed, in cancer vaccines is not contemplated in this review.

The disclosure of the instant application and the state of art establish that CpG immunostimulatory nucleic acids are effective in inducing antigen-specific and non-antigen-specific immune responses *in vitro* and *in vivo* including in human subjects. The claimed nucleic acids induce antigen-specific immune responses when administered with a viral antigen in a mouse model. The Examiner has provided no reasonable basis to doubt that the claimed nucleic acids would not similarly induce an antigen-specific response when combined with a cancer antigen.

### III. Conclusion.

In summary, Applicant respectfully traverses the rejection for a number of reasons. First, the Examiner has improperly read into the pending claims a functional limitation (i.e., treatment of cancer) that is not recited in the claims. Second, by requiring proof of cancer treatment, the Examiner has applied a legally untenable enablement standard to the pending composition claims. Third, the Examiner has ignored the fact that the pending claims are directed to nucleic acids comprising a consensus sequence to which immunostimulatory activity is attributed. Fourth, the Examiner has given no weight to the evidence of immunostimulation provided in the

specification. Fifth, the Examiner has not provided any evidence of having considered all the Wands factors in their totality. Instead the Examiner appears to have based the enablement rejection on a lack of predictability in the art. Since no one factor is dispositive in a proper Wands analysis, such emphasis is improper.

Reconsideration and withdrawal of the rejection is respectfully requested.

**CONCLUSION**

A Notice of Allowance is respectfully requested. **The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.**

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,



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